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(71)(72) Applicants and Inventors: KOCH, Martin [DK/DK]; Højbovej 11, DK–2500 Valby (DK). WOLF, Bernhard [DE/DE]; Andreasstrasse 12, D–79252 Stegen (DE). STETTER, Ernst [DE/DE]; Hoehenstrasse 5, D–64342 Seeheim (DE).

(74) Common Representative: KOCH, Martin; Højbovej 11, DK–2500 Valby (DK).

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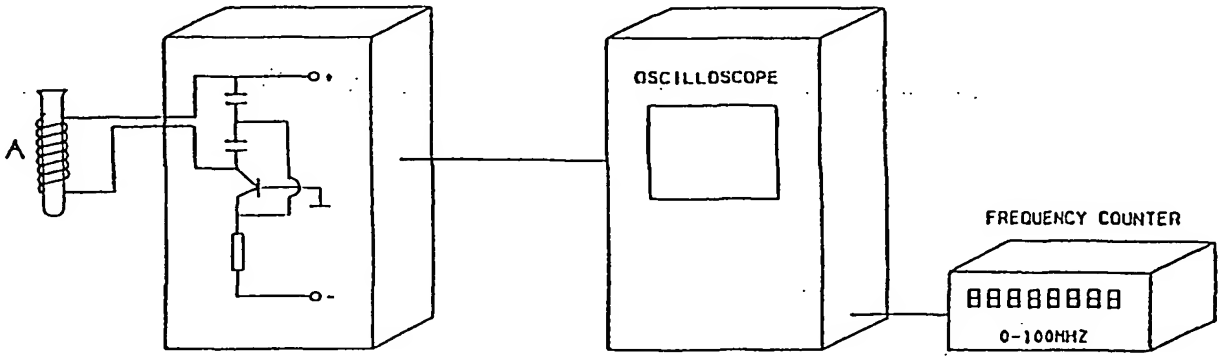
(54) Title: A NON–INVASIVE PROCEDURE AND AN APPARATUS FOR DETERMINING THE HEMOGLOBIN CONTENT OF BLOOD



(57) Abstract

A non–invasive procedure for determining the hemoglobin content of blood plus apparatus for accomplishing the procedure. The invention relates to a magnetic procedure to evaluate the paramagnetic liquid blood, through the use of magnetic ac fields, penetrating the blood samples. After the blood volume is detected, the magnetic material constant is evaluated by high selective oscillator circuits and very fast electronics. This offers a gentle non–invasive evaluation method for the hemoglobin content in the blood used in order to measure changes in oxygen supply or to detect internal bleeding.

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A non-invasive procedure and an apparatus for determining the hemoglobin content of blood.

The invention relates to a method for non-invasive determination of the content of a magnetic material such as hemoglobin in a deoxydated state in red blood cells by using a magnetic field e.g. as a method to detect the oxygen supply in the body.

State of the art

In order to determine the hemoglobin contents of the blood and the oxygen contents, it is possible to use a blood sample and a photometric method. However such methods require use of blood samples involving risk of contamination and infections.

US patent No. 4,539,994 discloses a transcutaneous measurement of blood gas partial pressure using an electro chemical measuring system adhered to the skin. The skin is heated during measurement.

At present in principle four methods are available for the measurement of magnetic properties of substances:

1) The well known and simplest method using a dc-magnetic-field to evaluate the permeability of paramagnetic liquids, is disclosed in Gerthsen/Kneser. Physik,Springer Verlag Berlin. Heidelberg, New York, Zehnte Auflage 1969
(freely translated into english)... in order to measure the permeability of paramagnetic liquids. the following procedure can be used: If one side of an U-vessel containing this liquid is put between the pole shoes of an

electromagnet, the liquid level in this side of the vessel will rise...

2) The highfrequent resonance procedures, e.g. MRI, ESR , ESE . There are many publications relating to this subject, just to name some:
Wertz and Bolton, Electronic Spin Resonance (1972)
Abragam and Bleaney, Elektron Paramagnetic Resonance of Transition Ions (1970)
Such techniques are concerned as the imaging of the interior of the body and do not depend on the magnetic properties of the blood.

3) Use of non-invasive electromagnetic flow meters to measure blood flow rates is disclosed in GB 1446063 and GB 1365129. However, they work by applying magnetic fields to the blood flowing through the body and detecting voltages on electrodes in contact with the skin. These voltages (U_h = Hall-Voltages) are produced because the blood is an electrolyte and opposite electric charges move in different directions in a homogeneous magnetic field, due to U_h.

4) US patent Nos. 4,079,730 and 3,980,076 disclose procedures concerning the measurement of diamagnetic susceptibility in the body using "squid's" (superconducting quantum interference devices). These measurements are affected by the diamagnetic properties of blood but are not primarily concerned with measuring hemoglobin content.

The resonance – systems together with others such as photometers provide the ability to study very small samples often producing extraordinary resolution and

discrimination between special species. Unfortunately they have to operate at very high frequencies e.g. ENDOR to ca. 150 GHz. EPR spectrometers in the range of 9-10 GHz to ca. 100 GHz. This makes their magnetic ac fields dependend on enviromental material constants, thereby preventing their use as non-invasive systems to evaluate the hemoglobin content of moving red blood cells.

Though independent from enviromental material constants, the above mentioned dc-method is obviously not able to evaluate the hemoglobin content of moving red blood cells in bodies non-invasively either.

Hall effects are produced due to the Lorentz force F_L,

$$\mathbf{F_L} = q\,(\mathbf{v_q} \times \mathbf{B}),\quad E_o = 0.$$

In connection with Hall effects magnetic flux density vector **B** is normally understood as constant and homogeneous. In flowmeter techniques mentioned in 3) a constant **B** should be applied, but it must be considered, that F_L expresses the relativity of induction effects.

All substances, whether magnetic or not, are diamagnetic if magnetic fields are applied. Diamagnetic induction effects are measured non-invasively with "squid" devices mentioned under 4). Here susceptibility becomes negative and the permeability is therefore less than one.

The non-invasive hemoglobin evaluation method of the invention can be better understood using Maxwells first equation (J.Clerk Maxwell, On Faraday's Lines of Force, Scientific papers 1855, 1856, reprinted Dover, New

York,1952, J.Clerk Maxwell, A Dynamical Theory of the Elektromagnetic Field, Scientific papers, 1864, J.Clerk Maxwell, Treatise on Electricity and Magnetism, Oxford, 3 rd. edition 1891), where the displacement term of the sum can be neclected. The method can therefore be called magnetic and is neither known nor obvious in view of the known techniques.

The application of magnetic fields, in order to evaluate the hemoglobin content of moving red blood cells in the body, is neither described nor indicated in the present state of art.

The above mentioned methods using dc-magnetic fields, combinations of dc/ac - fields and high frequent electromagnetic fields or rely, like the "squids", on Maxwells second equation.

General background in connection with the non-invasive procedure for determining the hemoglobin content of blood plus apparatus for accomplishing the procedure.

Using J.C.Maxwells equations the description of all electromagnetic aspects are possible according to G.Bosse, Gundlagen der Elektrotechnik II, B.I. Mannheim, Zürich, 1967. It is therefore possible to measure the magnetic capacity of substances e.g. iron. Iron is an essential element for life and every conceivable mechanism is used to enable the cell to come into possession of this mundane but biologically precious metal (B.Frankel/R.P.Blakemore, Iron Biominerals, Plenum Press 1991). A very large number of red blood cells (rbc´s) per volume blood contain many millions of hemoglobin molecules. The hemoglobin molecules occupy approximately one quarter of the space in a single rbc. Hemoglobin absorbs visible light strongly....only red

is transmitted, giving hemoglobin ist characteristic colour....hemoglobin contains unpaired electrons, when it is in the " deoxy state " (D.Eisenberg/D.Crothers, Physical Chemistry with application to life science, Cumming Publishing Company,94025 Cal.).

The invention is based on the finding that blood in its paramagnetic state can be evaluated non-invasively via a magnetic field circuit.

Measurements of magnetic fields in wetted porous clay materials as disclosed in WO 95/19217 deliver paramagnetic material constants which in a way proved Erwin Schrödingers statement from 1944 "Order out of disorder" or: If systems are forced out of of their balance condition, every possible way is used to counteract the applied gradients (Michael Murphy and Luke O`Neill, Was ist Leben? Die Zukunft der Biologie, Spektrum Akademischer Verlag 1997).

Further calculations and hereto related "double-blind experiments" – has shown, how microscopic systems can be interfered in order to produce macroscopic reactions in relation to de Haas/Einstein and Schrödinger.

Differences in comparism to systems already existing and system description.

The non-invasive procedure for determining the hemoglobin content of blood according to the invention utilizes a low-frequent magnetic field and may be described through Maxwell`s first equation neclecting the displacement. The method described in 1) is evaluating the relative height of a paramagnetic liquid column and can therefore only use dc-fields. The systems mentioned in 2) have to work in resonance with the objects they focus upon, e.g. electron spin and consequently high frequency magnetic fields must be applied . The methods in 3) and 4) obeying the Lenz- Rule.

A magnetic field circuit - understood as a self contained closed field with no sources - is established by a coil system. The magnetic lines of force produce a magnetic flux across a vessel containing a paramagnetic liquid which is placed in the magnetic path of the field. The magnetic flux-field gradients (Bronstein-Semendjajew, Taschenbuch der Mathematik, 6.Auflage, Verlag für Technisch Theoretische Literatur, Moskau 1965) can affect magnetic particles in such a liquid and the paramagnetic susceptibility can be measured. To evaluate these effects means however to work highly selective and this is only possible by applying electronic circuits. It has been found that as compared to qualitative methods, very fast conclusive measurements lasting only a fraction of the time of classical medical methods are possibly multiplying potential measurement capacities.

The object of the invention is to provide a method which results in non-invasive, compact and cost-effective measurement devices for in vitro, in vivo and - if required

– in situ measurements of the content of hemoglobin in red blood cells.

The present invention relates to a procedure for the evaluation of contents of a magnetic material in blood in which is used a magnetic field which penetrates the blood. It has been found that the contents of hemoglobin in its "deoxy state" may be determined quantitatively and accurately by measuring the change of oscillator supply current using a magnetic field. Such a measurement is carried out directly with a minimum change of the physiological conditions at the side of measurement and thus gives the results from a system being disturbed in a very low degree.

It has been found that very accurate and reliable results are obtained when the magnetic field is a static ac field or a dynamic ac field produced by using a single coil system or a multiphase coil system for the field production.

It is preferred that the coil system is embedded in a magnetic material as this renders the system more sensible.

In the most preferred embodiment of the procedure according to the invention, the magnetic field circuit is closed across the sample containing the magnetic material to be measured.

The invention also relates to an apparatus for the determination of a magnetic material as a blood component which apparatus comprises a frequency generator providing a magnetic field which penetrates a blood sample and highly selective oscillator circuits together with fast working electronics for detecting the change of the field and a sensor area for placing a sample.

The apparatus preferably comprises one coil system or a multiphase coil system for producing the magnetic field as a static ac field or a dynamic ac field enabling an

accurate and reliable determination of the contents of hemoglobin content in blood.

The apparatus preferably comprises a one phase– or a multi phase coil system embedded in a magnetic material being more sensible.

The apparatus according to the invention preferably comprises a part having a pair of tongs or pincers-like parts for gripping around and gently squeezing a superficial vein enabling a direct, non-invasive measurement not disturbing the tissue or flow being measured.

One or both pincing parts of the apparatus according to the invention may be movable and are preferably pressed towards each other by a spring force.

The method is disclosed more in detail with references to the drawings.

Fig.1 describes an experiment performed to prove quantitative aspects and to indicate predictable macroscopic reactions produced via microscopic magnetic effects. A transparent plastic box was mounted above an apparatus, as described in WO95/19217, producing a moving magnetic field, e.g. moving from left to right. A number of minute ferromagnetic particles considered as point particles were placed in this box. Under the influence of a dynamic magnetic field produced outside and beneath the box these particles gathered in small groups and rotated longitudinally, hereby demonstrating, that it is possible to disturb a microscopic multibodysystem in such a way, that detectable macroscopic dynamic reactions are provoked. Scientifically this has been demonstrated in double blind experiments which produced consistent results.

By using magnetic ac- or dynamic magnetic ac-fields the hemoglobin evaluation method differes from the existing methods mentioned above. Antoon Lorentz in the 1895 paper called his force , " die elektrische Kraft ". The forces used in flow meters described by A.Lorentz as "elektrische Kraft" are electric forces, but forces according to this invention are magnetic forces. The gradients built up in ferro- or paramagnetic substances by working this invention are gradients of magnetic fields e.g. grad B_1 B_2 (Bronstein, ibid) .

Fig.2 illustrates a laboratory experiment performed to prove the viability of the basic concept of the invention, i.e. evaluation of a paramagnetic liquid using electronic circuits.

The same principle will also apply for a non-invasive in vivo measurement of the paramagnetic permeability of a blood probe. In such a case no blood sample is placed

inside the coil but a vein is held in immediate vicinity of the coil at one side (A) of the coil.
A blood sample was installed within an oscillator circuit in such a way, that the sample appears as an inductance change in comparism to the air cored coil circuit and the frequency values counted represent relative to the cero values (air cored coil) the paramagnetic iron ion content in the heme group of hemoglobin.
The oscillator-solenoid was 50 mm long, with an inner diameter of 7.8 mm and 5 windings (Ar/Cu) with a wire-diameter of 0.9 mm . The active part of the oscillator was a transistor type FET BF 245 B. The oscillator set must be assembled in this way, that stable frequencies are produced. Despite a relatively high working frequency (app. 50 MHz) very stable frequency counts were produced.
In Fig.3 another practical example of an in vitro measurement of the paramagnetic susceptibility of a blood probe is shown, but the solenoid was embedded in a ferrit core. This core had a cylindrical opening in its centre to hold the blood samples. The coil was slightly changed (20 windings (Cu)) and the transistor was a type MPS 918 with a working frequency of app. 5 Mhz . The frequency counts were stable and reproducible but with a two order better differential compared with the 50 MHz oscillator. Fig.4 indicates the ferrit core containing the solenoid.
This embodiment is preferred as it provides more accurate results.

The magnetic field used according to the invention can be produced by a microcomputer controlled apparatus containing a solenoid (Fig.5). A ferrit assembly located where the main magnetic force field is spread along, establishes a flux across the probe, closing the magnetic

field with low losses. The solenoid which is required to produce the magnetic-probe field, should preferably be placed in a ferromagnetic material, in order to produce a field gain, increasing hereby the efficiency of the connected oscillator circuit. The material containing magnetic fields, must be produced in such a way, that eddy currents. induced by the magnetic field, are avoided. A multiphase coil system, mounted in magnetic material can also be applied for field-production. Then the magnetic field will gain a dynamical characteristic as disclosed in WO 95/19217 and because of the electronically controlled production of the field the speed and direction may be changed dynamically, introducing the possibility of fast relative measurements.

Each red blood cell (rbc) contains app. 280×10^6 hemoglobin (Hb) molecules, each Hb molecule has 4 heme groups and each heme group has a central Fe^{2+}- ion having 4 unpaired electrons on the 3d shell in the magnetic state. There are approximately $5 \times 10^6 mm^{-3}$ rbc's in the human blood compared with the elefants $3.8 \times 10^6 mm^{-3}$ rbc's.

When the magnetic field passes through the blood, magnetic hemoglobin molecules, normally located inside the erythrocytes, are affected by the magnetic field, and the inductor-inductance of the oscillator-cirquit is slightly changed. This can be detected through fast frequency counts of changing oscillator resonance frequencies.

Changes in the capillary hemoglobin content, e.g. caused by inner bleeding, can also be detected by the device described above (Fig.5).

The results may be processed through microcontrollers evaluating and selecting the data to be displayed.

In one embodiment of the invention the sensors for non-invasive hemoglobin measurements are connected to modularly established subsystems containing display units. The solenoid part of the oscillator can be embedded in magnetic material.
In another embodiment of the invention, multiple sensor systems for non-invasive hemoglobin measurements containing multiphase coil systems are used, in order to establish dynamic magnetic ac-fields.
In a preferred embodiment of the invention the power supply, oscillator circuits, microcontrollers and display unit are integrated into one compact device which can be easily operated by a large group of end users.

Fig. 5 shows an embodiment of the invention in the form of different integrated device sensors for the non-invasive in situ measurement of veneous hemoglobin. These sensors between which is shown a vein consist, e.g. of a flexible two component material containing magnetic material with a paramagnetic characteristic comparable to ferrit in relation to permeability. Because these sensors are flexible they can be adjusted to fit the sample. The equipment automatically adjust for sample volume. The device may be used for direct determination of hemoglobin in blood by placing the sensors gently squeezing a superficial vein e.g. at the back of the hand.

Fig. 6 indicates another practical application for the device (Fig.5). Oxygen moves from the blood across the capillary walls into the tissue. This movement is driven by the difference of oxygen concentration between blood and tissue (Ann I. Baldwin, Oxygen Delivery from Blood to the Muscle Fibers,Dept. Of Physiology, University of Arizona, 1.30.97). The evaluation of the paramagnetic blood content of the capillaries e.g. in the ear lobe will

not only produce excellent results, but the device can also be used to detect internal bleedings in emergency medicin e.g. to be used by a paramedical at the side of an accident.

Patent Caims

1. A procedure for the evaluation of contents of a magnetic material in blood, in which is used a low frequent magnetic field which penetrates the blood, by measuring the change of resonance frequency by fast frequency counts of the changing resonance frequencies

2. A procedure according to claim 1 characterized in that the magnetic field is a static ac field or a dynamic ac field produced by using a single coil system or a multiphase coil system for the field production.

3. A procedure according to claim 2, characterized in that a coil system embedded in a magnetic material is used.

4. A procedure as claimed in claim 2 or 3, characterized in that the magnetic field circuit is closed across the sample containing a magnetic material.

5. An apparatus for the determination of a magnetic material as a blood component, using a low frequent magnetic field which penetrates the blood, characterized in that it comprises a frequency generator providing a magnetic field which penetrates a blood sample and highly selective oscillator circuits together with fast working electronics for detecting the change of the field.

6. An apparatus as claimed in claim 5 characterized in that it comprises one coil system or a multiphase coil

system for producing the magnetic field as a static ac field or a dynamic ac field.

7. An apparatus according to claim 5 or 6, characterized in that it comprises a one phase– or a multi phase coil system embedded in a magnetic material.

8. An apparatus according to any of claims 5-7, characterized in that it has a sensor area placed in a closed magnetic field circuit.

9. An apparatus according to claim 8 characterized in that the sensor area is placed between a pair of projecting tongs.

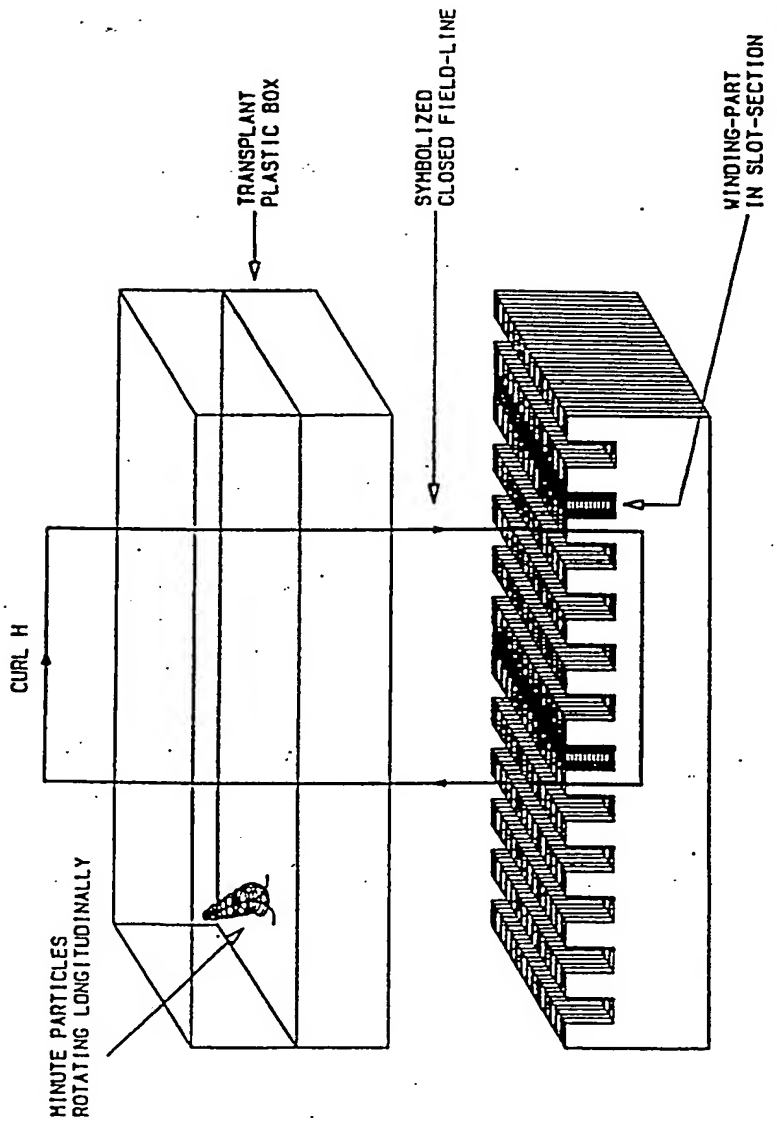

TRANSPLANT
PLASTIC BOX
SYMBOLIZED
CLOSED FIELD-LINE
WINDING-PART
IN SLOT-SECTION
CURL H
MINUTE PARTICLES
ROTATING LONGITUDINALLY

FIG. 1

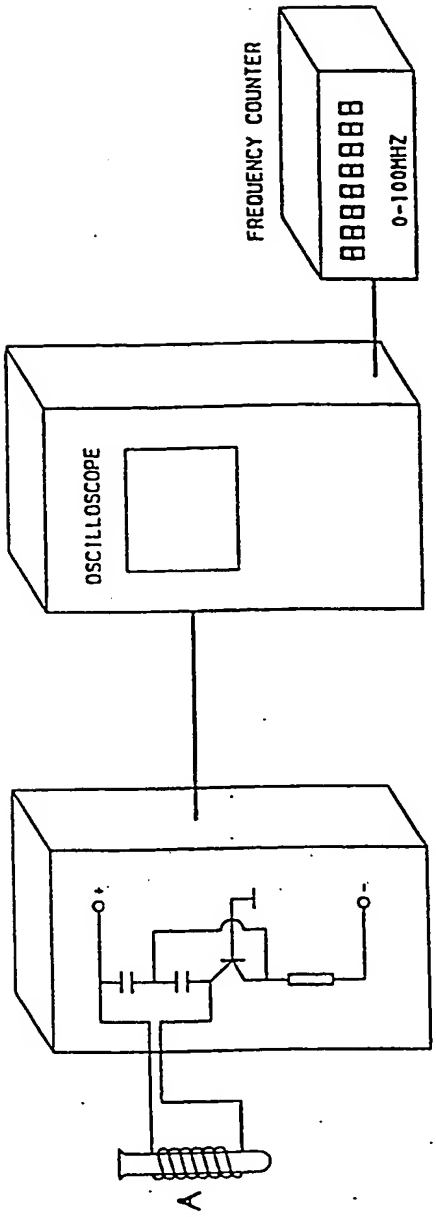


FIG.2

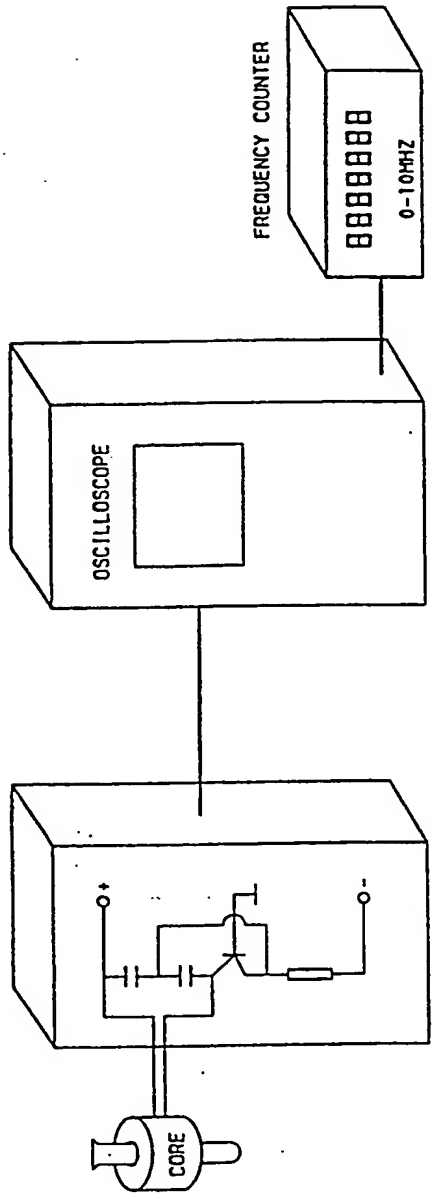
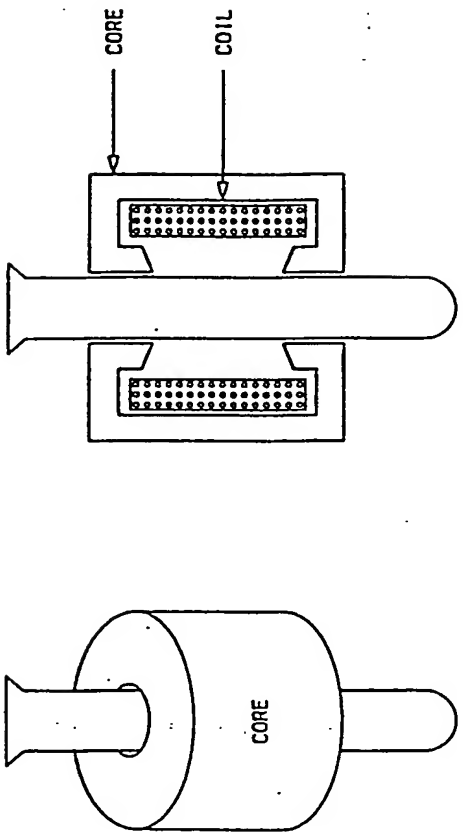


FIG.3



$$\text{GRAD } B = \left(\frac{\partial Bx}{\partial x}, \frac{\partial By}{\partial y}, \frac{\partial Bz}{\partial z}\right)$$

FIG.4

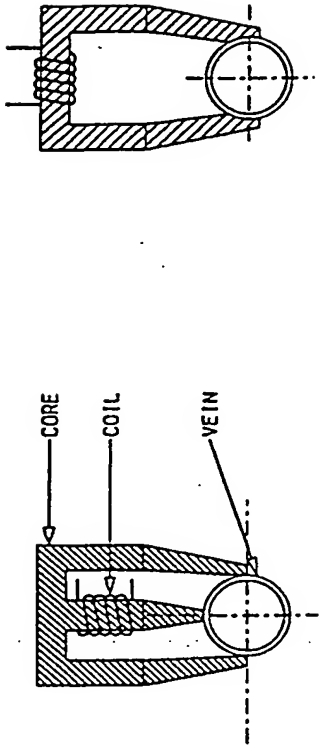


FIG.5

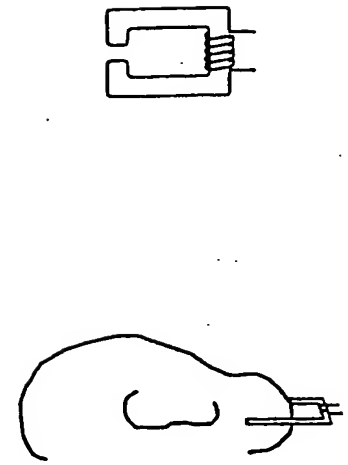


FIG.6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00172

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61B 5/05, A61B 5/145, G01N 33/49
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61B, G01N, G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5323776 A (DOUGLAS M. BLAKELEY ET AL), 28 June 1994 (28.06.94), column 1, line 30 - line 56; column 4, line 26 - line 58, abstract --	1-9
A	GB 2207510 A (MANCHESTER LASERS LIMITED), 1 February 1989 (01.02.89), page 2, line 10 - page 3, line 8; page 4, line 15 - page 6, line 28, figure 1, claims 1,3, abstract --	1-9
A	US 5233991 A (GRAHAM A. WRIGHT), 10 August 1993 (10.08.93), column 1, line 8 - column 2, line 68, figures 1,2, abstract --	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5325728 A (DOUGLAS J. ZIMMERMAN ET AL), 5 July 1994 (05.07.94), column 12, line 23; page 34, abstract --	1-9
A	US 4984574 A (SETH GOLDBERG ET AL), 15 January 1991 (15.01.91), column 2, line 50 - line 63; column 3, line 62 - column 4, line 26; column 6, line 22 - line 45, column 7, line 41 - line 59, figure 5, abstract --	1
A	GB 875710 B (NATIONAL RESEARCH DEVELOPMENT CORPORATION), 23 August 1961 (23.08.61), page 1, line 8 - line 26; page 1, line 49 - page 2, line 18; page 2, line 37 - line 54, figures 1-3, claim 1 -- --------	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

08/05/00

International application No.
PCT/DK 00/00172

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5323776 A	28/06/94	NONE	
GB 2207510 A	01/02/89	AU 2081488 A WO 8900702 A	13/02/89 26/01/89
US 5233991 A	10/08/93	NONE	
US 5325728 A	05/07/94	NONE	
US 4984574 A	15/01/91	EP 0455851 A	13/11/91
GB 875710 B	23/08/61	NONE	